Cell Genomics Transparent Peer Review Record

Genome-wide risk prediction of common diseases across ancestries in one million people

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Summary

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Data freely available:	see STAR Methods
Code freely available:	see STAR Methods

Referees' reports, first round of review

Reviewer #1:

This nicely written manuscript develops polygenic risk scores (PRS) for CAD, T2D, and breast and prostate cancer, and investigate the PRS transferability across global populations and within different European populations (in six large biobanks). They found that PRS derived primarily from European GWAS were strongly associated with the diseases across all European populations, regardless of the varying health care systems and geographic subpopulations; the PRS effect sizes for disease were smaller in non-European populations. A major strength of this study is its exploration of PRS transferability in multiple large-scale cohorts. That said, the general findings reported here parallel previously reported findings across more 17 traits (Martin et al. 2019 Nat Gen). Moreover, the results are somewhat limited, and further analyses are needed to fully characterize the effect size differences across and within populations for each of the phenotypes.

Specific comments.

1. Further details on the PRS should be provided. For example, the LDpred parameters were optimized in an independent FinnGen population. How if at all does this impact the PRS effect size estimates that are observed? Would different parameter choices result in better transferability?

2. Previous work indicates that PRS transferability varies between South and East Asian ancestry populations (Martin et al. 2019 Nat Gen). In light of this, it seems like these populations should be analyzed separately.

3. Supplemental Figure 1 shows that the effect sizes within the African ancestry and Asian ancestry populations vary significantly by cohort. The authors should consider presenting these results rather than the pooled results in Figure 1.

4. Given the large cohort size, it seem worthwhile to examine PRS transferability as a function of admixture proportions—rather than across the entire ancestry group—as the average effect size may be misleading.

5. Methods Lines 12-18. How do the results change if PRS are constructed from only variants that overlap with the GWAS across the different biobanks?

6. In light of the large, diverse biobanks reported here with diverse populations

7. Although previous GWAS were primarily in European populations, the biobanks reported here have large, diverse populations. In light of this, it would seem worthwhile to test additional PRS building approaches using non-European data (e.g., using cross-validation or splitting populations into training and testing sets).

8. The paper concludes that the patterns observed here hold across "different healthcare settings". While this is true for the populations investigated, they may or may not hold across different healthcare settings in general.

Reviewer #2:
This concise paper examines the performance of polygenic risk scores generated in European populations when applied to European and non-European ancestry populations. The authors find that, similar to previous examinations of the same topic, PRS perform worse in non-European populations. However, the scale of the data sets used in this work are substantially larger than those used in previously published papers. I have the following suggestions:

It would be useful to have a formal statistical test for differences in PRS effect sizes between populations. This is true for both claims of difference (e.g. between continental populations) and claims of similarity (e.g. withing Finland).

The authors build PRS from the software package LDPred, which is now outdated. Given the opportunity afforded by the data sets available it would be interesting to see a more contemporary approach used. LDPred2, for example, has marked improvement over LDPRed.

https://academic.oup.com/bioinformatics/advance-article/doi/10.1093/bioinformatics/btaa1029/6039173

This large collection also seems like a perfect opportunity to examine recent approaches for transferring PRS between populations. For example: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5726434/

Reviewer #3:

The paper represents relatively straightforward evaluation of PRS for four major diseases across different global biobanks consisting of different ancestry populations (East Asian and African). The paper is well written and easy to follow. Methods used are sound.

While overall the study population is large, the sample size for the AA population is fairly limited specially if one considers the number of cases of breast and prostate cancer. The findings generally corroborate what is known about performance of EA-derived PRS in other populations and this study adds to the literature. One novel aspect of the study is the demonstration of robust performance of PRS across different population genetic background of individuals within Finland. I only have a few comments.

1) Line 13-24. Please provide relevance citations for papers that have shown utility of PRS beyond clinical risk scores for these diseases.

2) The paper is missing citations of some recent papers that have evaluated performance of breast cancer PRS across different ancestry groups (see below). I have not checked for other diseases for missing references.

3) Discussion. Page 8, First paragraph: "Our results highlighting the differences between risk estimates between ancestry group are in line with earlier small scale reports".

While this current study seems very large because of size of the European populations, in fact for non-EA populations, such as the AA population, this study

is fairly limited. Results from more powerful studies with larger number of cases are already reported in the literature. For example, for prostate cancer, the paper by Conti et al. (citation 31) has evaluated the performance of PRS in multiple non-EA populations, with much larger number of cases than this study which only has ~300 cases for the African ancestry population. Similarly, for breast cancer, several papers have now come out evaluating the performance of EA-derived PRS in multiple non-EA populations with much larger number of cases (PMID: 32737321, PMID: 31553449; PMID: 33769540). The current study has only ~200 cases of breast cancer in African ancestry population and has low power. Published study show that EA-derived PRS do have predictive ability in African ancestry population though as observed for other traits, performance drop substantially compared to the EA populations.

4) Methods. All of the PRS were derived from the LD-pred method which retains potentially millions of SNPs in the models. While complex PRS with large number of SNPs may perform better than more parsimonious PRS in the training population (ie EA population), for transferability to another population this may not necessarily be the case in our experience. It is possible that top SNPs with the largest effects could be more transferrable across populations, while large number of SNPs each with minuscule effects may be more population specific. I would suggest that for each trait the authors also evaluate performance of more parsimonious EA-derived PRS based on top SNPs (e.g 313 SNP PRS for Breast Caner developed by the BCAC group) across other ethnic groups.

Authors' response to the first round of review

Comments to the Editors:
We thank the Reviewers for the constructive feedback, which has helped to improve the manuscript considerably. The major changes include completely new analyses of crossancestry comparison of polygenic risk scores derived with different methodologies, improvements in reporting of results across ancestries and expanding references to previous research. Please find below point-by-point author responses to the comments.

Reviewers' Comments:
Reviewer #1: This nicely written manuscript develops polygenic risk scores (PRS) for CAD, T2D, and breast and prostate cancer, and investigate the PRS transferability across global populations and within different European populations (in six large biobanks). They found that PRS derived primarily from European GWAS were strongly associated with the diseases across all European populations,

regardless of the varying health care systems and geographic subpopulations; the PRS effect sizes for disease were smaller in non-European populations. A major strength of this study is its exploration of PRS transferability in multiple large-scale cohorts. That said, the general findings reported here parallel previously reported findings across more 17 traits (Martin et al. 2019 Nat Gen). Moreover, the results are somewhat limited, and further analyses are needed to fully characterize the effect size differences across and within populations for each of the phenotypes.

Author response:
We would like to thank the reviewer for the feedback and we agree that our major strength is in combining data across multiple large-scale biobanks and cohorts. Compared to previous studies, and as highlighted by the Reviewer, we would in addition highlight a key strength our focus on four diseases for which PRSs have shown promise for clinical utility (based on e.g. PMIDs 29789686, 25855707, 32273609). Finally, we study the behaviour of the clinically relevant PRSs on three levels of potential genetic heterogeneity: across global ancestries, across different cohorts of European ancestry, and across a country with well-known population bottleneck resulting in genetic differences along an East-West gradient. We therefore believe that our results are of major importance when considering future clinical applications of PRSs to prevent common complex diseases. Although Martin et al (Nat Gen 2019) and other studies have reported similar findings, their focus was not on disease risks but rather on the behaviour of PRSs on blood and anthropometric traits, with less immediate relevance on clinical utility across broadly defined ancestry groups. To our knowledge there are far fewer studies done on common diseases, particularly studies using the state-of-the-art genome-wide PRSs.

Based on the feedback, we have now added three new analyses to further characterize the effects within and across ancestries and discuss the impact of the results on the potential application of PRSs in clinical settings. We have separated individuals of East and South Asian ancestry in our main results, included an UK Biobank analysis showing effects across ancestries for different LDpred parameters, and added a new analysis comparing PRSs derived with different methodologies across ancestries.

Specific comments.
1. Further details on the PRS should be provided. For example, the LDpred parameters were optimized in an independent FinnGen population. How if at all does this impact the PRS effect size estimates that are observed? Would different parameter choices result in better transferability?

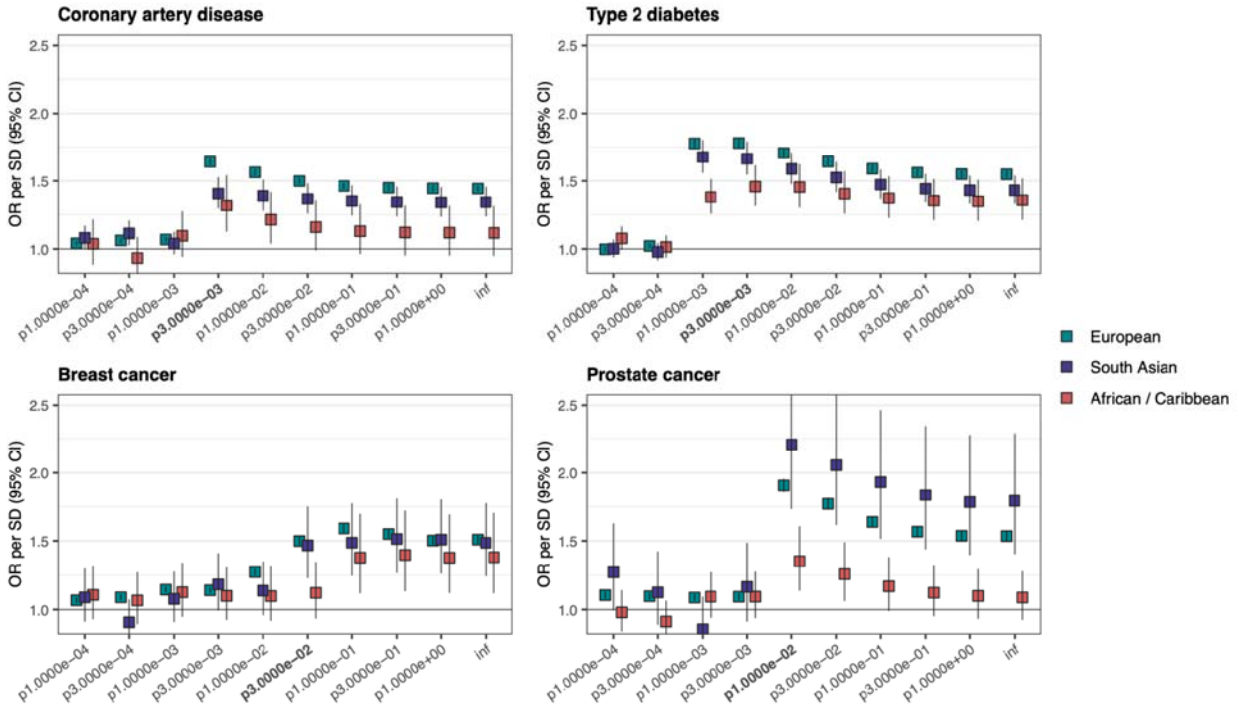
Author response: Based on this comment, we have now added a new Supplementary Figure 1 (below for reference), which shows the effects across ancestries for the different LDpred parameters. In individuals of European ancestry, the differences between the parameters was small. For individuals of South Asian or African ancestry, the differences were mostly small, but for breast cancer, the choice of the parameter had a large impact on effect size, displaying a significant drop compared to higher fractions of causal variants (i.e. proportion of genetic variants LDpred assumes to be causal).

This is a great addition to the manuscript, and the results on page 5 now reads as follows: *" In breast cancer, we did not detect an association for women of African ancestry (OR 1.12, 95% CI 0.93–1.35 in UK Biobank, OR 0.90, 0.69–1.35 in MGB Biobank), but looking at the effects across different LDpred parameters for fraction of causal variants in UK Biobank (Supplementary Figure 1), the PRS would be associated with OR 1.40 (1.13-1.72), had the fraction been chosen based on individuals of African ancestry, instead of individuals of European ancestry. In other diseases, the choice of the fraction had only a fairly small effect."*

While doing this analysis, we observed a small error in our UK Biobank analysis on

prostate cancer. In all other cohorts and biobanks, we had used the correct fraction of causal variants p = 0.01 for prostate cancer, but in UK BIobank, we had used the causal variants for breast cancer (p = 0.03) in analyses on prostate cancer in UK Biobank. We have now fixed this in Figure 1 and in Supplementary Table 1, resulting in moderate improvements in the performance of the prostate cancer PRS in UK Biobank (OR 1.77 -> 1.91 for European ancestry; OR 2.06 -> 2.21 for South Asian ancestry; OR 1.26 -> 1.35 in African / Caribbean ancestry).

Supplementary Figure 1. Effect sizes across ancestries with the different LDpred fractions of causal variants. Odds ratios (OR) with 95% confidence intervals (CI) are shown for 1-SD increase in the polygenic risk scores. The fraction of causal variants used in the main analyses are bolded.

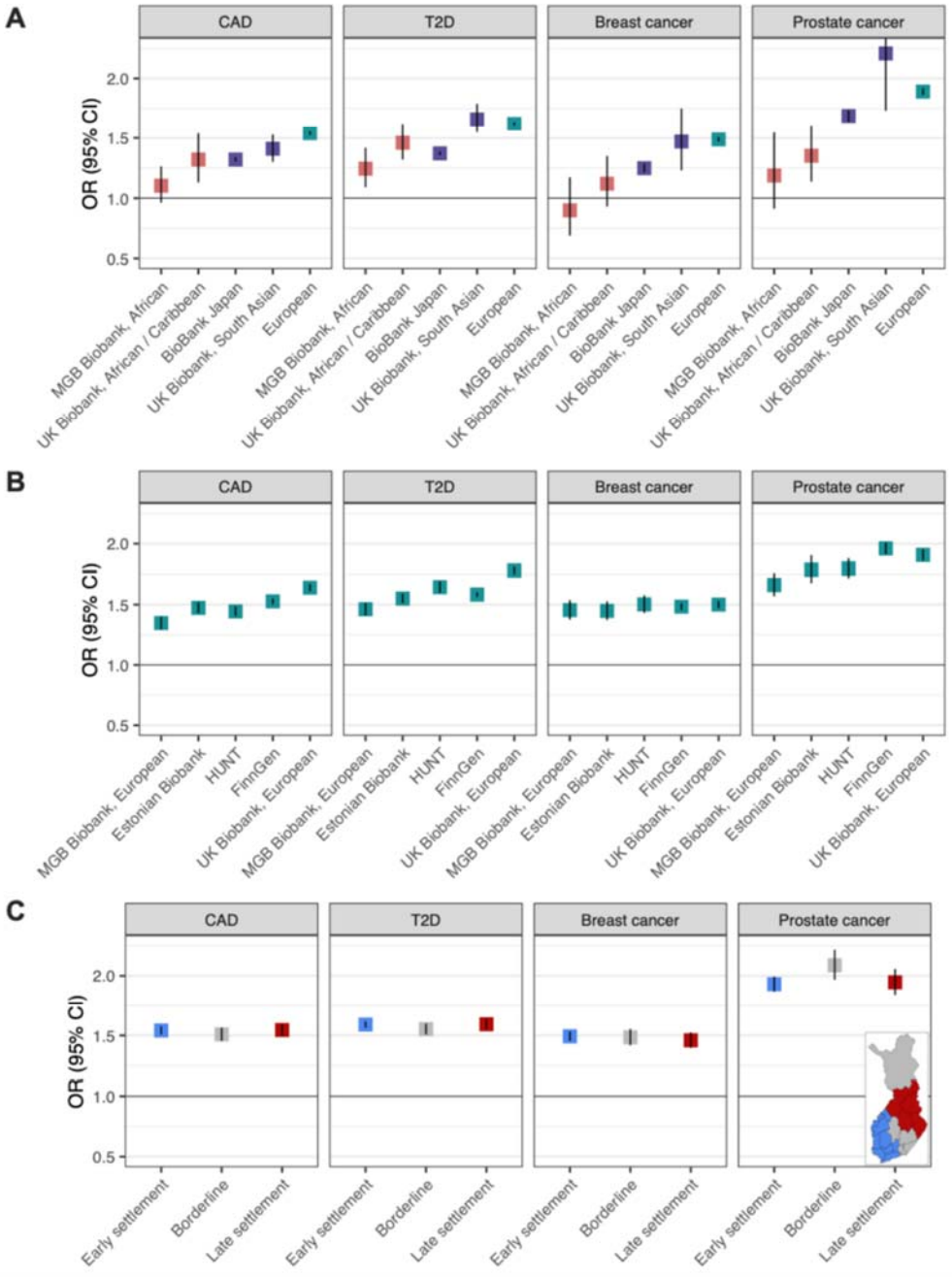


2. Previous work indicates that PRS transferability varies between South and East Asian ancestry populations (Martin et al. 2019 Nat Gen). In light of this, it seems like these populations should be analyzed separately.
3. Supplemental Figure 1 shows that the effect sizes within the African ancestry and Asian ancestry populations vary significantly by cohort. The authors should consider presenting these results rather than the pooled results in Figure 1.

Author response: Comments #2 and #3 are addressed jointly. We agree with the Reviewer, and have now separated results of individuals of South and East Asian ancestry in Figure 1 and Supplementary Table 1. In line with Reviewer's comment #3, we show the results also

separately by cohort. Figure 1 is shown below for reference.

Figure 1. Odds ratios (OR) with 95% confidence intervals (CI) are shown for 1-SD increase in the polygenic risk scores. **Panel A** shows the results across ancestry groups, with 'European' representing a pooled OR of effect sizes from panel B. **Panel B** shows the results across different populations with European ancestry and **panel C** across in early- and late-settlement regions in Finland (FinnGen).

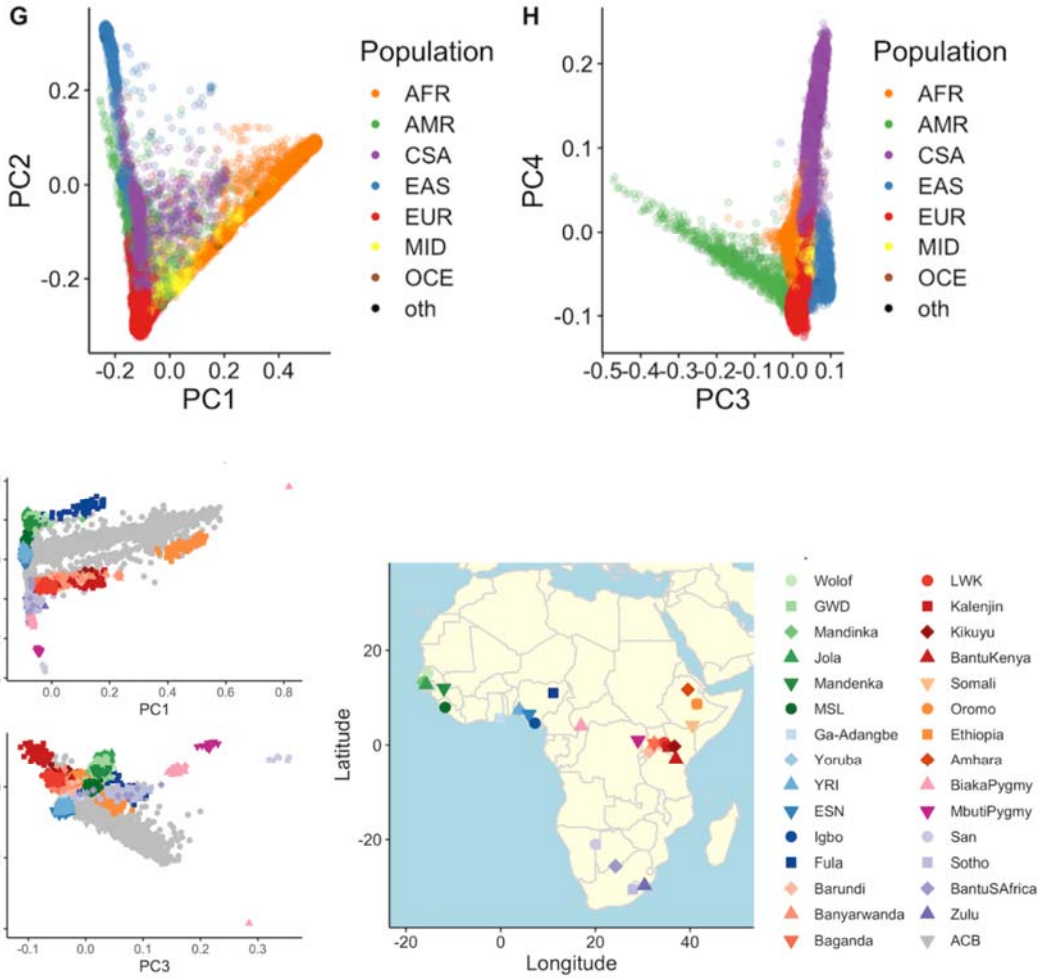


4. Given the large cohort size, it seem worthwhile to examine PRS transferability as a function of admixture proportions—rather than across the entire ancestry group—as the average effect size may be misleading.

Author response: We agree with the reviewer that this is a valid aspect of assessing PRS

transferability, but consider there to be two main challenges with respect to our study. The first challenge is that our study focuses on binary traits (four diseases with broad public health importance), which leads to much lower power than if we had studied quantitative traits. The case counts are fairly small particularly for individuals of South Asian or African ancestry, and would most likely be even smaller if we would assess admixture proportions. For instance, number of cases in South Asians was 139 for breast cancer and 72 for prostate cancer, being only slightly lower in the cohorts with individuals of African ancestry.

Secondly, how to define ancestry consistently across biobanks is generally still work in progress. For these reasons, this questions are perhaps be better answered by independent projects and manuscripts using quantitative traits, such as https://pubmed.ncbi.nlm.nih.gov/32878958/ and https://www.biorxiv.org/content/10.1101/2021.01.12.426453v1. For instance, the plots below obtained from the latter preprint assessing PRS accuracy across African ancestries shows a in individuals of African ancestry mix of West African and European ancestry, as well as continental heterogeneity. Figures G-H) show the global ancestry assignments for UK Biobank participants based on reference panel meta-data labels. Figures B-C) show subcontinental ancestry principal components in the African ancestry assigned group (AFR) in UK Biobank.



In terms of individuals of European ancestry, our Figure 1B and 1C panels give some indirect answer to the question, as they imply that although the overall genetic differences between populations with European ancestry are quite large (e.g European-ancestry

individuals in Finland vs Boston), this does not translate into big differences in PRS risk estimates as long as the PRSs are scaled separately in each cohort.
We have now added the comment about admixture into the limitations paragraph in the Discussion, saying "*While our comparisons show relatively small differences between cohorts with European ancestry, it may be that the risk estimates vary considerably between individuals due to for example admixed ancestry and the role of admixture in this variability warrants further research*."

5. Methods Lines 12-18. How do the results change if PRS are constructed from only variants that overlap with the GWAS across the different biobanks?

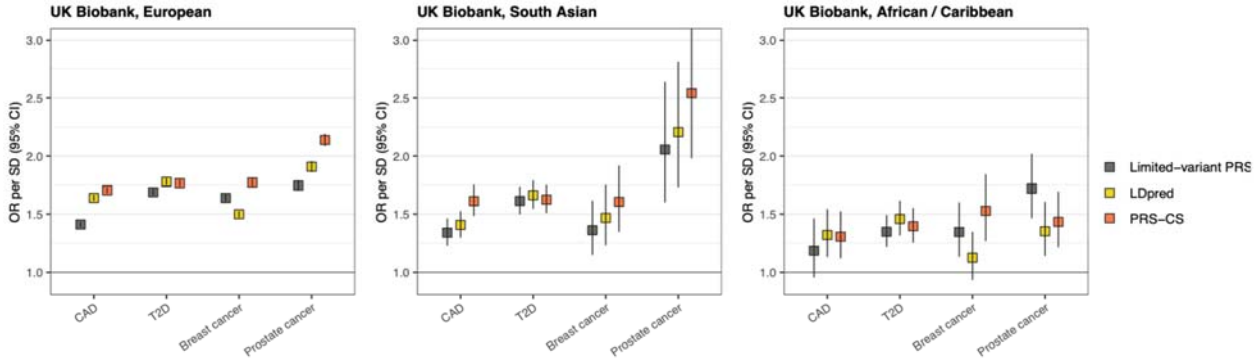
**Author response: We agree that the set of variants may differ between datasets (due to dataand ancestry-related factors such as difference in allele frequencies), and this may have an impact particularly on transferability across ancestries. With this study, we aimed at using a setting as similar as possible to real-life situations, where the generation of PRSs does not include optimization based on variant overlap of various ancestry groups. We have now added to the Method details on page 12 the following sentence: *"To perform the analysis in a setting as similar as possible to clinical use cases, where variant optimization cannot always be done for the derivation and test sets, we did not seek to optimize variant overlap between datasets."* However, several of the newer tools overcome this challenge by building genome-wide PRSs restricting the analyses to HapMap3 variants, which are high-quality common variants with high availability in most datasets due to being polymorphic in most populations. Examples of such tools include PRS-CS and LDpred2. We have now added an analysis comparing genome-wide PRSs generated with PRS-CS, comparing the effects across ancestries in UK Biobank (Figure 2, shown for reference below). For the PRS-CS PRSs, the transferability was highly similar across ancestries. Detailed effect size comparisons are in Supplementary Table 3, which is also shown for reference below. We have added two paragraphs reporting the results from this analysis to Results on pages 5 and 6, and one paragraph to Methods on page 13. The results are discussed on page 8. The Results reads as follows: *"Lastly, we compared in UK Biobank the LDpred PRSs to two other types of PRSs generated primarily in individuals of European ancestry: 1) to previously published PRSs containing a smaller number of variants[3, 10, 17, 18] and 2) to genome-wide PRSs generated with PRS-CS, which restricts analyses to HapMap3 variants (Figure 2, Supplementary Table 3). In both European and South Asian ancestry, the highest effect size was observed in 3/4 diseases for PRS-CS (CAD, breast cancer and prostate cancer). In T2D, the effect sizes were fairly similar across the three PRSs. In African / Caribbean ancestry, the best-performing PRS varied by disease: in CAD, the LDpred and PRS-CS had the highest and highly similar effects; in T2D, LDpred had the highest effect size but the difference between the different PRSs were fairly small; in breast cancer, the PRS-CS PRS had the highest effect size, with a considerable drop (to 27% of the effect size) with the LDpred PRS and a moderate drop to 70% for the limitedvariant PRS; in prostate cancer, the smaller PRS had the highest effect size, with considerable effect size drops with the other PRSs.*

Looking at the transferability of the different CAD PRSs across ancestries in UK Biobank (Figure 2, Supplementary Table 3), the best transferability was observed for the PRSCS PRS (drop to 90% for South Asian ancestry, and to 56% for African / Caribbean ancestry, compared to European ancestry). For the T2D PRSs, the transferability between PRSs was highly similar (drops to 85–91% for South Asian ancestry and to 58%–65% for African / Caribbean ancestry). For the breast cancer PRSs, the best transferability to South Asian ancestry was observed for the LDpred PRS (drop to 95%) and for the PRS-CS PRS (drop to 83%), with a drop to 62% for the small PRS. For the breast cancer PRSs, the best transferability to African / Caribbean ancestry was observed for the PRS-CS PRS (drop to 74%), followed by the small PRS (drop to 60%). For prostate cancer PRSs, the best and similar

transferabilities to South Asian ancestry were observed for the PRS-CS and LDpred PRSs, but the best transferability to African / Caribbean ancestry was observed for the smaller PRS."

Discussion, page 8: *"The genome-wide PRSs were also compared to the PRSs containing a smaller number of variants. In general, the genome-wide PRSs, particularly PRSs generated with PRS-CS, conferred the largest effect sizes. Compared to the PRSs containing a smaller number of variants, the genome-wide PRSs showed generally better performance and higher transferability to individuals of South Asian and African ancestry. The main exception was African ancestry, where the prostate cancer PRS consisting of 269 variants outperformed the LDpred and PRS-CS PRSs. One reason for this may be that the GWAS underlying the 269 PRS is highly diverse, containing multiple cohorts of individuals of African ancestry,[18] whereas in the other PRSs across the diseases, the GWAS was primarily based on individuals of European ancestry. This finding further highlights the need for more diversity in genetic discovery studies, and the need for research on optimizing trans-ancestry polygenic risk prediction. This finding further highlights the need for more diversity in genetic discovery studies, and the need for research on optimizing trans-ancestry polygenic risk prediction."*

Figure 2. Comparison of three types of polygenic risk scores (PRS) in UK Biobank: previously published PRSs using a smaller number of variants ('limited-variant PRS'),[3,10,17,18] PRSs generated with LDpred, and PRSs generated with PRS-CS. Odds ratios (OR) with 95% confidence intervals (CI) are shown across ancestries for 1-SD increase in the PRS. Detailed effect size comparisons are in **Supplementary Table 3**.



CAD = coronary artery disease, T2D = type 2 diabetes.

Supplementary Table 3. Comparison of polygenic risk scores (PRS) developed with different methodologies, tested in UK Biobank. The decreases in effect sizes were calculated from regression estimates (betas).

	OR	95% CI	Decrease in effect size compared to European ancestry	Decrease in effect size compared to PRS-CS in European ancestry	Decrease in effect size compared to PRS-CS in South Asian ancestry	Decrease in effect size compared to PRS-CS in African / Caribbean ancestry
Coronary artery disease						
Limited-variant PRS						
European	1.41	1.39-1.43	Ref	64 %		
South Asian	1.34	1.23-1.46	85 %		61 %	
African / Caribbean	1.18	0.96-1.46	49 %			63 %
LDpred PRS						
European	1.64	1.61-1.67	Ref	93 %		
South Asian	1.41	1.30-1.53	69 %		71 %	
African / Caribbean	1.32	1.13-1.54	56 %			104 %
PRS-CS PRS						
European	1.70	1.68-1.73	Ref	Ref		
South Asian	1.61	1.48-1.75	90 %		Ref	
African / Caribbean	1.30	1.12-1.52	56 %			Ref
Type 2 diabetes						
Limited-variant PRS						
European	1.69	1.66-1.72	Ref	92 %		
South Asian	1.61	1.50-1.74	91 %		98 %	
African / Caribbean	1.35	1.22-1.49	57 %			89 %
LDpred PRS						
European	1.78	1.75-1.81	Ref	101 %		
South Asian	1.66	1.55-1.79	88 %		105 %	
African / Caribbean	1.46	1.32-1.62	65 %			113 %
PRS-CS PRS						
European	1.77	1.74-1.80	Ref	Ref		
South Asian	1.63	1.51-1.75	85 %		Ref	
African / Caribbean	1.40	1.25-1.55	58 %			Ref
Breast cancer						
Limited-variant PRS						
European	1.64	1.61-1.67	Ref	86 %		
South Asian	1.36	1.14-1.62	62 %		65 %	
African / Caribbean	1.34	1.13-1.60	60 %			70 %
LDpred PRS						
European	1.50	1.47-1.53	Ref	71 %		
South Asian	1.47	1.23-1.75	95 %		81 %	
African / Caribbean	1.12	0.93-1.35	28 %			27 %
PRS-CS PRS						
European	1.77	1.74-1.81	Ref	Ref		
South Asian	1.61	1.35-1.92	83 %		Ref	
African / Caribbean	1.53	1.27-1.84	74 %			Ref
Prostate cancer						
Limited-variant PRS						
European	2.20	2.14-2.25	Ref	97 %		
South Asian	2.06	1.60-2.64	92 %		77 %	
African / Caribbean	1.72	1.46-2.02	69 %			151 %
LDpred PRS						
European	1.91	1.86-1.96	Ref	85 %		
South Asian	2.21	1.73-2.81	123 %		85 %	
African / Caribbean	1.35	1.14-1.61	47 %			84 %
PRS-CS PRS						
European	2.14	2.09-2.19	Ref	Ref		
South Asian	2.54	1.98-3.26	123 %		Ref	
African / Caribbean	1.43	1.21-1.69	47 %			Ref

6. In light of the large, diverse biobanks reported here with diverse populations

Author response: We unfortunately did not understand the comment, and were therefore unable to address it. Perhaps this was related to the next comment?

7. Although previous GWAS were primarily in European populations, the biobanks reported here have large, diverse populations. In light of this, it would seem worthwhile to test additional PRS building approaches using non-European data (e.g., using cross-validation or splitting populations into training and testing sets).

Author response: We believe that our strength is in the large-scale evaluation genome-wide PRSs generated with existing tools, and doing this across different levels of ancestry (across global ancestries, across different cohorts of European ancestry, and across a country with well-known East-West differences). Splitting into training and testing sets would require broad access to individual-level data, and rerunning the GWAS. Although our dataset comprises diverse populations, we would have limited statistical power for building PRSs based on diverse ancestries, as the power of PRSs are highly dependent on the number of cases in the primary GWAS. Moreover, it is unclear how to best split the datasets into target and training sets, and cohort-specific strategies may be needed. After the GWAS, it is not clear what would be the optimal strategy for combining cohorts of diverse ancestries, and which LD panel to use for generating the PRS. For these reasons, we believe this questions would be more thoroughly answered by separate projects, particularly as the there are multiple ongoing efforts to improve PRS methodology for cross-ethnic polygenic prediction, such as PRS-CSx https://www.medrxiv.org/content/10.1101/2020.12.27.20248738v1, IMPACT https://www.nature.com/articles/s41588-020-00740-8, and PolyPred https://www.medrxiv.org/content/10.1101/2021.01.19.21249483v1, which will help future studies to test additional PRS building approches for genome-wide PRSs.

8. The paper concludes that the patterns observed here hold across "different healthcare settings". While this is true for the populations investigated, they may or may not hold across different healthcare settings in general.

Author response: We agree that the generalizability of this study is limited to populations and healthcare settings included in the study. We have now changed the abstract accordingly, and the abstract conclusions now reads as follows: *"Our findings indicate that in the populations investigated, the current genome-wide polygenic scores for common diseases have potential for clinical utility within different healthcare settings for individuals of European ancestry, but that the utility in individuals of African ancestry is currently much lower."* In other parts of the manuscript, we are more careful in the wording related to the healthcare settings. For instance, in the limitations section in the discussion, we highlight that *" - - differences in risk between ancestries may arise from a range of factors, including socioeconomic and healthcare system-related factors - -".*

Reviewer #2: This concise paper examines the performance of polygenic risk scores generated in European populations when applied to European and non-European ancestry populations. The authors find that, similar to previous examinations of the same topic, PRS perform worse in non-European populations. However, the scale of the data sets used in this work are substantially larger than those used in previously published papers. I have the following suggestions:

Author response: Let us first note that we appreciate considerably the set of suggestions of the reviewer, which have provided more rigor to the comparisons across ancestries, and across different types of polygenic risk scores.

Regarding the formal testing of the differences between effects sizes, we have now included a p-value of heterogeneity for test of heterogeneity (based on Cochran's heterogeneity statistic) to Supplementary Table 2. The evidence from this analysis is line with the conclusions of our study. To summarize, the comparison across global ancestries reflects the fairly small sample size for some of the datasets, with most heterogeneity observed for T2D (p-value = 7.38e-06) which also had the largest case counts across ancestries. The comparison across datasets of European ancestry showed heterogeneity for CAD (p = 3.55e-28), T2D (p = 3.48e-35), and prostate cancer (p = 2.91e-07), but the effects were similar in breast cancer (p = 0.63). The comparisons within Finland indicated similar effects (p = 0.56 for CAD, p = 0.32 for T2D, p = 0.70 for breast cancer and p = 0.07 for prostate cancer).

It would be useful to have a formal statistical test for differences in PRS effect sizes between populations. This is true for both claims of difference (e.g. between continental populations) and claims of similarity (e.g. withing Finland).

Author response: We have now included a p-value of heterogeneity for test of heterogeneity (based on Cochran's heterogeneity statistic) to Supplementary Table 2. The evidence from this analysis is line with the conclusions of our study. To summarize, the comparison across global ancestries reflects the fairly small sample size for some of the datasets, with most heterogeneity observed for T2D (p-value = 7.38e-06) which also had the largest case counts across ancestries. The comparison across datasets of European ancestry showed heterogeneity for CAD (p = 3.55e-28), T2D (p = 3.48e-35), and prostate cancer (p = 2.91e-07), but the effects were similar in breast cancer (p = 0.63). The comparisons within Finland indicated similar effects (p = 0.56 for CAD, p = 0.32 for T2D, p = 0.70 for breast cancer and p = 0.07 for prostate cancer).

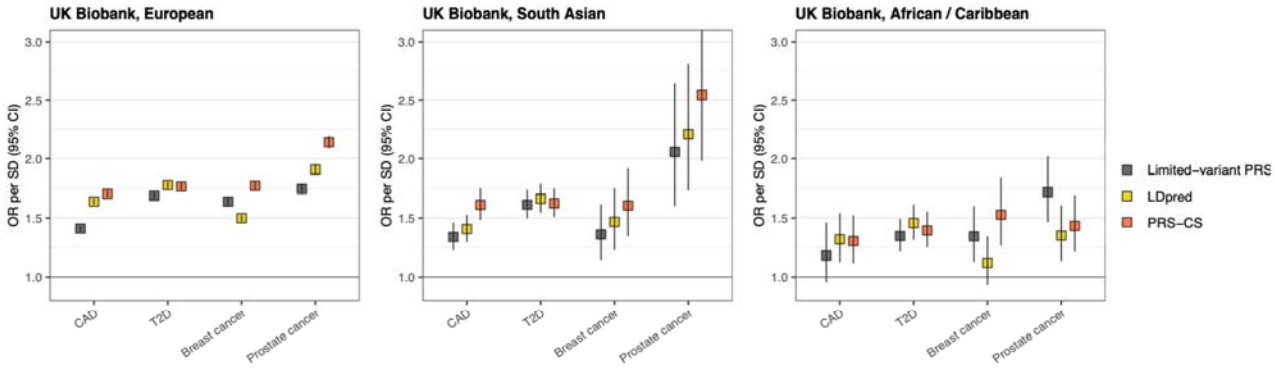
The authors build PRS from the software package LDPred, which is now outdated. Given the opportunity afforded by the data sets available it would be interesting to see a more contemporary approach used. LDPred2, for example, has marked improvement over LDPRed.
https://academic.oup.com/bioinformatics/advancearticle/
doi/10.1093/bioinformatics/btaa1029/6039173

Author response: We agree that despite the expanding use of LDpred with good results, newer and even better software have been published, such as LDpred2 and PRS-CS. Based on the reviewers' feedback, we have now added an analysis with PRSs made with a more contemporary software (PRS-CS). For the PRS-CS PRSs, we observed transferability was highly similar across ancestries as we observed for the LDpred PRSs, but with slightly higher effect sizes. Figure 2 with these results is shown below for reference, with detailed effect sizes reported in Supplementary Table 3. We have added two paragraphs reporting the results from this analysis to Results on pages 5 and 6, and one paragraph to Methods on page 13, and a paragraph to the Discussion on page 8.

Results: ***"Lastly, we compared in UK Biobank the LDpred PRSs to two other types of PRSs generated primarily in individuals of European ancestry: 1) to previously published PRSs containing a smaller number of variants[3, 10, 17, 18] and 2) to genome-wide PRSs generated with PRS-CS, which restricts analyses to HapMap3 variants (Figure 2, Supplementary Table 3). In both European and South Asian ancestry, the highest effect size was observed in 3/4 diseases for PRS-CS (CAD, breast cancer and prostate cancer). In T2D, the effect sizes were fairly similar across the three PRSs. In African / Caribbean ancestry, the best-performing PRS varied by disease: in CAD, the LDpred and PRS-CS had the highest and highly similar effects; in T2D, LDpred had the highest effect size but the difference between the different PRSs were fairly small; in breast cancer, the PRS-CS PRS had the highest effect size, with a considerable***

drop (to 27% of the effect size) with the LDpred PRS and a moderate drop to 70% for the limited-variant PRS; in prostate cancer, the smaller PRS had the highest effect size, with considerable effect size drops with the other PRSs.
Looking at the transferability of the different CAD PRSs across ancestries in UK Biobank (Figure 2, Supplementary Table 3), the best transferability was observed for the PRSCS PRS (drop to 90% for South Asian ancestry, and to 56% for African / Caribbean ancestry, compared to European ancestry). For the T2D PRSs, the transferability between PRSs was highly similar (drops to 85–91% for South Asian ancestry and to 58%–65% for African / Caribbean ancestry). For the breast cancer PRSs, the best transferability to South Asian ancestry was observed for the LDpred PRS (drop to 95%) and for the PRS-CS PRS (drop to 83%), with a drop to 62% for the small PRS. For the breast cancer PRSs, the best transferability to African / Caribbean ancestry was observed for the PRS-CS PRS (drop to 74%), followed by the small PRS (drop to 60%). For prostate cancer PRSs, the best and similar transferabilities to South Asian ancestry were observed for the PRS-CS and LDpred PRSs, but the best transferability to African / Caribbean ancestry was observed for the smaller PRS."
Discussion, page 8: *"The genome-wide PRSs were also compared to the PRSs containing a smaller number of variants. In general, the genome-wide PRSs, particularly PRSs generated with PRS-CS, conferred the largest effect sizes. Compared to the PRSs containing a smaller number of variants, the genome-wide PRSs showed generally better performance and higher transferability to individuals of South Asian and African ancestry. The main exception was African ancestry, where the prostate cancer PRS consisting of 269 variants clearly outperformed the LDpred and PRS-CS PRSs. One reason for this may be that the GWAS underlying the 269 PRS is highly diverse, containing multiple cohorts of individuals of African ancestry,[18] whereas in the other PRSs across the diseases, the GWAS was primarily based on individuals of European ancestry. This finding further highlights the need for more diversity in genetic discovery studies, and the need for research on optimizing trans-ancestry polygenic risk prediction."*

Figure 2. Comparison of three types of polygenic risk scores (PRS) in UK Biobank: previously published PRSs using a smaller number of variants ('limited-variant PRS'),[3,10,17,18] PRSs generated with LDpred, and PRSs generated with PRS-CS. Odds ratios (OR) with 95% confidence intervals (CI) are shown across ancestries for 1-SD increase in the PRS. Detailed effect size comparisons are in **Supplementary Table 3**.



CAD = coronary artery disease, T2D = type 2 diabetes.

This large collection also seems like a perfect opportunity to examine recent approaches for transferring PRS between populations. For example:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5726434/

Author response: The Reviewer raises an important point, but as discussed in our response to Reviwer #1 comment #7, although our dataset comprises diverse populations, we would consider the dataset fairly small for building PRSs based on diverse ancestries for disease phenotypes, particularly in individuals of South Asian or African ancestry. Additional challenges include also open questions about the optimal way to divide diverse cohorts and ancestries into target and training sets, the best ways to combine results across diverse

ancestries, and questions related to choice of LD panel for generating the PRS. For these reasons, we believe this questions would be more thoroughly answered by separate projects, particularly as the there are multiple ongoing efforts to improve PRS methodology for crossethnic polygenic prediction, such as PRS-CSx https://www.medrxiv.org/content/10.1101/2020.12.27.20248738v1, IMPACT https://www.nature.com/articles/s41588-020-00740-8, and PolyPred https://www.medrxiv.org/content/10.1101/2021.01.19.21249483v1, which will help future studies to test additional PRS building approches for genome-wide PRSs.

In the revised version of the manuscript, we have added further novelty to the analyses by comparing different types of PRSs across ancestries, as described in our response to the previous comment. Very few such analyses have been published particularly across several diseases, and the published studies have looked at CAD, such as Dikilitas et al 2020 (PMID 32386537) which compared four PRSs for CAD, including one made with LDpred. The CAD PRS made with LDpred was also compared across ancestries in a recent brief report by Fahed et al (PMID 33284643).

Reviewer #3: The paper represents relatively straightforward evaluation of PRS for four major diseases across different global biobanks consisting of different ancestry populations (East Asian and African). The paper is well written and easy to follow. Methods used are sound.
While overall the study population is large, the sample size for the AA population is fairly limited specially if one considers the number of cases of breast and prostate cancer. The findings generally corroborate what is known about performance of EA-derived PRS in other populations and this study adds to the literature. One novel aspect of the study is the demonstration of robust performance of PRS across different population genetic background of individuals within Finland. I only have a few comments.

Author response: We appreciate the feedback and agree that the sample size for individuals of African ancestry is fairly low despite the large total sample size of the study. To further highlight this, we now start the limitations paragraph in the discussion with the sentence *"Despite the large number of individuals studied, the sample size in South Asian or African ancestries remained fairly small, particularly for analyses on breast and prostate cancer."* The changes made based on the feedback have added an aspect of novelty to the study, by adding a comparison to previously published PRSs containing a smaller number of variants. Although the contemporary PRSs have focused on liberalizing variant inclusion, few comparisons exist across ancestries, particularly looking at individuals of African Ancestry.
1) Line 13-24. Please provide relevance citations for papers that have shown utility of PRS beyond clinical risk scores for these diseases.

Author response: This is an important observation and we regret for omitting these in the previous version. We have now added references to the sentence "We evaluated the variability of the PRS risk estimates across multiple populations and ancestry groups in four common complex diseases which have shown promise beyond routinely used clinical risk scores:

coronary artery disease (CAD), type 2 diabetes (T2D), breast cancer and prostate cancer.[2, 6-10]"
The selected references are:

2. Mars N, Koskela JT, Ripatti P, Kiiskinen TTJ, Havulinna AS, Lindbohm JV, et al. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers. Nat Med. 2020.
6. Lee A, Mavaddat N, Wilcox AN, Cunningham AP, Carver T, Hartley S, et al. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. Genet Med. 2019;21(8):1708-18.
7. Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, et al. Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults: Implications for Primary Prevention. J Am Coll Cardiol. 2018;72(16):1883-93.
8. Hindy G, Aragam Krishna G, Ng K, Chaffin M, Lotta Luca A, Baras A, et al. Genome-Wide Polygenic Score, Clinical Risk Factors, and Long-Term Trajectories of Coronary Artery Disease. Arterioscler Thromb Vasc Biol. 2020;40(11):2738-46.
9. Yanes T, Young MA, Meiser B, James PA. Clinical applications of polygenic breast cancer risk: a critical review and perspectives of an emerging field. Breast Cancer Res. 2020;22(1):21.
10. Lall K, Magi R, Morris A, Metspalu A, Fischer K. Personalized risk prediction for type 2 diabetes: the potential of genetic risk scores. Genet Med. 2017;19(3):322-9.

2) The paper is missing citations of some recent papers that have evaluated performance of breast cancer PRS across different ancestry groups (see below). I have not checked for other diseases for missing references.

Author response: We are aware that several studies evaluating performance across ancestries have been done for PRSs containing a small number of variants. The breast cancer research community has been particularly active in this field, many studies testing the PRS containing 313 SNPs, or a smaller number of variants. As we show in the new analysis comparing different PRSs, the limited-variant scores are not optimal ways to capture the risks. For breast cancer, the PRS-CS score outperforms the 313 SNP score in all ancestries.
However, the highly polygenic PRSs made with more contemporary software contain a much larger number of variants, and have in several studies demonstrated improved performance over PRSs containing a small number of variants, but most of these studies have been done in individuals of European ancestry. Only a few studies comparing such PRSs have been published particularly across several diseases, and the published studies have mostly evaluated CAD PRSs, such as Dikilitas et al 2020 (PMID 32386537) which compared four PRSs for CAD, including one made with LDpred.
The PMID 32737321 (Ho et al. 2020) is reference number 19. We are also aware of the great study by Shieh et al (PMID 31553449), but had previously not referred to it as our study does not include US Latinas and Latin American. We have now included it as reference number 20. We have now added a reference to the study by Du et al (PMID 33769540, now as reference 22), published soon after the submission of this manuscript. Overall, we have now added several new references, and changed the second paragraph of the Discussion to highlight the novelty of this manuscript, i.e. the usage of genome-wide PRS:
Discussion, page 7: *"Several studies have looked at trans-ancestry performance of PRSs for common diseases, but the majority of such studies have used PRSs containing a small number of variants, consisting of approximately tens to a few hundred genetic variants.[18-29] Contemporary PRSs have focused on liberalizing variant inclusion to build genome-wide PRSs, which typically contain hundreds of thousands to a few million variants.[30-33] but only few studies have assessed transferability of such PRSs across ancestries,[34-36] with even fewer comparing these genome-wide PRSs to ones containing a smaller number of variants.[31, 34, 37] To our knowledge, this is the largest study to date evaluating these genomewide European-ancestry PRSs across ancestries, with additional evaluation of effects across*

different cohorts of European ancestry, and within a country with well-known East-West differences. Our order of effect sizes by ancestry — largest in Europeans, followed by South and East Asians, with generally lowest effect sizes detected in Africans – are consistent with population history, and are in line with the previous studies using a smaller number of variants, with further evidence from comparisons of prediction accuracy of anthropometric traits, and lipid biomarkers.[5, 19, 22, 24, 26, 34, 38, 39] "

3) Discussion. Page 8, First paragraph: "Our results highlighting the differences between risk estimates between ancestry group are in line with earlier small scale reports".
While this current study seems very large because of size of the European populations, in fact for non-EA populations, such as the AA population, this study is fairly limited. Results from more powerful studies with larger number of cases are already reported in the literature. For example, for prostate cancer, the paper by Conti et al. (citation 31) has evaluated the performance of PRS in multiple non-EA populations, with much larger number of cases than this study which only has ~300 cases for the African ancestry population. Similarly, for breast cancer, several papers have now come out evaluating the performance of EA-derived PRS in multiple non-EA populations with much larger number of cases (PMID: 32737321, PMID: 31553449; PMID: 33769540). The current study has only ~200 cases of breast cancer in African ancestry population and has low power. Published study show that EA-derived PRS do have predictive ability in African ancestry population though as observed for other traits, performance drop substantially compared to the EA populations.

Author response: We have now added this important limitation to the beginning of the limitations paragraph on page 9: *"Despite the large number of individuals studied, the sample size in South Asian or African ancestries remained fairly small, particularly for analyses on breast and prostate cancer."* We agree that several previous studies looking at transferability exist, particularly for the 313-SNP score on breast cancer.

4) Methods. All of the PRS were derived from the LD-pred method which retains potentially millions of SNPs in the models. While complex PRS with large number of SNPs may perform better than more parsimonious PRS in the training population (ie EA population), for transferability to another population this may not necessarily be the case in our experience. It is possible that top SNPs with the largest effects could be more transferrable across populations, while large number of SNPs each with minuscule effects may be more population specific. I would suggest that for each trait the authors also evaluate performance of more parsimonious EA-derived PRS based on top SNPs (e.g 313 SNP PRS for Breast Caner developed by the BCAC group) across other ethnic groups.

Author response: This is a very interesting question, and we have now added a comparison of the LDpred PRSs to previously published PRSs containing a smaller number of variants. This analysis was done across ancestries in UK Biobank. For this analysis, we chose for each disease one previously published PRS containing a more limited number of SNPs. The PGS Catalog IDs for the chosen PRSs are PGS000012 (Abraham et al. 2016), PGS000020 (Läll et al 2017), PGS000004 (Mavaddat et al. 2019), and PGS000662 (Conti & Darst et al 2021). The number of variants in UK Biobank (out of the variants in the original score) was 48,523/49,310 for CAD, 7,491/7,502 for T2D, 306/313 for breast cancer, and 267/269 for prostate cancer. Alongside this analysis, we also added a comparison to another genome-wide PRS made with a more contemporary software, PRS-CS. Overall, the PRS-CS PRSs showed better transferability across ancestries than both the LDpred PRSs and the smaller PRSs. The only exception was prostate cancer, where the new 269 SNP score outperformed the PRS-CS score in the African ancestry individuals. However, this is probably due to the multiethnic nature of the primary GWAS and highlights the need for multi-ancestry GWASes for better PRS transferability in other diseases as well.

The overall results are shown in Figure 2 with detailed effect sizes in Supplementary

Table 3 (both below for reference). We have made the following changes to the manuscript: We describe these analyses in detail in the methods on page 13, and have added the following two paragraphs to the Results: ***"Lastly, we compared in UK Biobank the LDpred PRSs to two other types of PRSs generated primarily in individuals of European ancestry: 1) to previously published PRSs containing a smaller number of variants[3, 10, 17, 18] and 2) to genomewide PRSs generated with PRS-CS, which restricts analyses to HapMap3 variants (Figure 2, Supplementary Table 3). In both European and South Asian ancestry, the highest effect size was observed in 3/4 diseases for PRS-CS (CAD, breast cancer and prostate cancer). In T2D, the effect sizes were fairly similar across the three PRSs. In African / Caribbean ancestry, the best-performing PRS varied by disease: in CAD, the LDpred and PRS-CS had the highest and highly similar effects; in T2D, LDpred had the highest effect size but the difference between the different PRSs were fairly small; in breast cancer, the PRS-CS PRS had the highest effect size, with a considerable drop (to 27% of the effect size) with the LDpred PRS and a moderate drop to 70% for the limited-variant PRS; in prostate cancer, the limited-variant PRS had the highest effect size, with considerable effect size drops with the other PRSs.***
Looking at the transferability of the different CAD PRSs across ancestries in UK Biobank (Figure 2, Supplementary Table 3), the best transferability was observed for the PRSCS PRS (drop to 90% for South Asian ancestry, and to 56% for African / Caribbean ancestry,

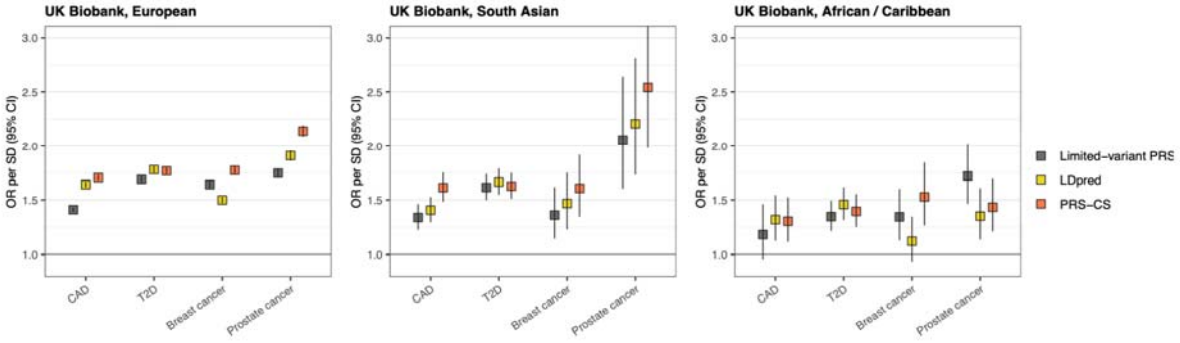
compared to European ancestry). For the T2D PRSs, the transferability between PRSs was highly similar (drops to 85–91% for South Asian ancestry and to 58%–65% for African / Caribbean ancestry). For the breast cancer PRSs, the best transferability to South Asian ancestry was observed for the LDpred PRS (drop to 95%) and for the PRS-CS PRS (drop to 83%), with a drop to 62% for the small PRS. For the breast cancer PRSs, the best transferability to African / Caribbean ancestry was observed for the PRS-CS PRS (drop to 74%), followed by the small PRS (drop to 60%). For prostate cancer PRSs, the best and similar transferabilities to South Asian ancestry were observed for the PRS-CS and LDpred PRSs, but the best transferability to African / Caribbean ancestry was observed for the smaller PRS."

Discussion, page 8: ***"The genome-wide PRSs were also compared to the PRSs containing a smaller number of variants. In general, the genome-wide PRSs, particularly PRSs generated with PRS-CS, conferred the largest effect sizes. Compared to the PRSs containing a smaller number of variants, the genome-wide PRSs showed generally better performance and higher transferability to individuals of South Asian and African ancestry. The main exception was African ancestry, where the prostate cancer PRS consisting of 269 variants clearly outperformed the LDpred and PRS-CS PRSs. One reason for this may be that the GWAS underlying the 269 PRS is highly diverse, containing multiple cohorts of individuals of African ancestry,[18] whereas in the other PRSs across the diseases, the GWAS was primarily based on individuals of European ancestry. This finding further highlights the need for more diversity in genetic discovery studies, and the need for research on optimizing trans-ancestry polygenic risk prediction."***

Summary, page 2, rows 10-12: ***"Comparing genome-wide PRS to PRSs containing a smaller number of variants, the highly polygenic, genome-wide PRSs generally displayed higher effect sizes and better transferability across global ancestries."***

Conclusions paragraph in Discussion, page 10, rows 21-22: ***"The highly polygenic, genome-wide PRSs generally displayed better transferability across ancestries than PRSs containing a smaller number of variants."***

Figure 2. Comparison of three types of polygenic risk scores (PRS) in UK Biobank: previously published PRSs using a smaller number of variants ('limited-variant PRS'), [3, 10, 17, 18] PRSs generated with LDpred, and PRSs generated with PRS-CS. Odds ratios (OR) with 95% confidence intervals (CI) are shown across ancestries for 1-SD increase in the PRS. Detailed effect size comparisons are in **Supplementary Table 3**.



CAD = coronary artery disease, T2D = type 2 diabetes.

Supplementary Table 3. Comparison of polygenic risk scores (PRS) developed with different methodologies, tested in UK Biobank. The decreases in effect sizes were calculated from regression estimates (betas).

	OR	95% CI	Decrease in effect size compared to European ancestry	Decrease in effect size compared to PRS-CS in European ancestry	Decrease in effect size compared to PRS-CS in South Asian ancestry	Decrease in effect size compared to PRS-CS in African / Caribbean ancestry
Coronary artery disease						
Limited-variant PRS						
European	1.41	1.39-1.43	Ref	64 %		
South Asian	1.34	1.23-1.46	85 %		61 %	
African / Caribbean	1.18	0.96-1.46	49 %			63 %
LDpred PRS						
European	1.64	1.61-1.67	Ref	93 %		
South Asian	1.41	1.30-1.53	69 %		71 %	
African / Caribbean	1.32	1.13-1.54	56 %			104 %
PRS-CS PRS						
European	1.70	1.68-1.73	Ref	Ref		
South Asian	1.61	1.48-1.75	90 %		Ref	
African / Caribbean	1.30	1.12-1.52	56 %			Ref
Type 2 diabetes						
Limited-variant PRS						
European	1.69	1.66-1.72	Ref	92 %		
South Asian	1.61	1.50-1.74	91 %		98 %	
African / Caribbean	1.35	1.22-1.49	57 %			89 %
LDpred PRS						
European	1.78	1.75-1.81	Ref	101 %		
South Asian	1.66	1.55-1.79	88 %		105 %	
African / Caribbean	1.46	1.32-1.62	65 %			113 %
PRS-CS PRS						
European	1.77	1.74-1.80	Ref	Ref		
South Asian	1.63	1.51-1.75	85 %		Ref	
African / Caribbean	1.40	1.25-1.55	58 %			Ref
Breast cancer						
Limited-variant PRS						
European	1.64	1.61-1.67	Ref	86 %		
South Asian	1.36	1.14-1.62	62 %		65 %	
African / Caribbean	1.34	1.13-1.60	60 %			70 %
LDpred PRS						
European	1.50	1.47-1.53	Ref	71 %		
South Asian	1.47	1.23-1.75	95 %		81 %	
African / Caribbean	1.12	0.93-1.35	28 %			27 %
PRS-CS PRS						
European	1.77	1.74-1.81	Ref	Ref		
South Asian	1.61	1.35-1.92	83 %		Ref	
African / Caribbean	1.53	1.27-1.84	74 %			Ref
Prostate cancer						
Limited-variant PRS						
European	2.20	2.14-2.25	Ref	97 %		
South Asian	2.06	1.60-2.64	92 %		77 %	
African / Caribbean	1.72	1.46-2.02	69 %			151 %
LDpred PRS						
European	1.91	1.86-1.96	Ref	85 %		
South Asian	2.21	1.73-2.81	123 %		85 %	
African / Caribbean	1.35	1.14-1.61	47 %			84 %
PRS-CS PRS						
European	2.14	2.09-2.19	Ref	Ref		
South Asian	2.54	1.98-3.26	123 %		Ref	
African / Caribbean	1.43	1.21-1.69	47 %			Ref

Other changes:
- **Supplementary Table 2: The number of controls for breast and prostate cancer in MGB Biobank and Estonian Biobank have been corrected (previous control numbers by mistake from men and women**

Referees' report, second round of review

Reviewer #1: No further comment.

Reviewer #2: Authors have addressed all my concerns.

Reviewer #3: Comments enter in this field will be shared with the author; your identity will remain anonymous.

The authors have done a nice job revising the paper. I am glad to see the comparison of transportability of alternative PRS, including those based on more limited number of variants.

My only concern of the paper is that I think the title is bit misleading as currently stands "Genomewide risk prediction of common diseases across ancestries in one million people". Given non-European ancestry data is a tiny fraction of the entire study, I feel the title, while catchy, it will make readers think this is truly a diverse study in a large population. The discussion mentions the limitation of small sample size for non-EA ancestry, but it is buried and it does not discuss the implications of small sample size. In particular large standard errors associated with PRS OR for non-EA population makes it hard to figure out the difference across populations/methods are real or by chance.

Authors' response to the second round of review

Reviewer #3: The authors have done a nice job revising the paper. I am glad to see the comparison of transportability of alternative PRS, including those based on more limited number of variants.

My only concern of the paper is that I think the title is bit misleading as currently stands "Genomewide risk prediction of common diseases across ancestries in one million people". Given non-European ancestry data is a tiny fraction of the entire study, I feel the title, while catchy, it will make readers think this is truly a diverse study in a large population. The discussion mentions the limitation of small sample size for non-EA ancestry, but it is buried

and it does not discuss the implications of small sample size. In particular large standard errors associated with PRS OR for non-EA population makes it hard to figure out the difference across populations/methods are real or by chance.

Author response: We appreciate the time and effort put in to reviewing our manuscript, which helped to improve the quality and content. Although the sample size for Asian ancestry is fairly large, particularly for East Asian ancestry (N = 178,726), we agree that the sample size for individuals of African ancestry is fairly small. To emphasize this, we have now revised the Summary to highlight this in the first sentence reporting results: *"All four PRSs had similar accuracy across European and Asian populations, with poorer transferability in the smaller group of individuals of African ancestry."* Moreover, the Discussion now contains on page 10 a subheading "Limitations of the study", with further points to this important limitation described in detail in the paragraph.